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Comments on Petition for Stay of Action
2004P-0140/PSA2

On behalf of King Pharmaceuticals, Inc. ("King"), the undersigned submit these comments on the Petition for Stay of Action filed by Mutual Pharmaceutical Company, Inc. on April 5, 2004. Mutual, one of the applicants seeking approval to market a generic metaxalone product that relies on King's SKELAXIN® as the reference listed drug, requests that FDA stay approval of all supplements for changes to SKELAXIN® labeling, including in particular, S-046, which is the subject of the Agency's March 12, 2004 approvable letter to King. Mutual proposes that the stay remain in effect until FDA has published proprietary clinical data and correspondence submitted to King's NDA and has considered comments on these materials and SKELAXIN® labeling, as well as the possibility of omitting information in SKELAXIN® labeling from the labeling for generic metaxalone.

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King opposes Mutual's Petition for Stay. As established below, neither the criteria for a mandatory nor a discretionary stay are satisfied in this case. Indeed, the purpose of the stay is to provide Mutual and others unprecedented access to confidential information in King's NDA and the opportunity to interfere in and delay FDA's evaluation of that material.

While King believes that the requested stay is improper and should be summarily denied, King does agree with Mutual on one point: FDA's determination of whether or not pharmacokinetic information describing the relative bioavailabilty of metaxalone when taken with or without food may be omitted from the labeling for generic metaxalone should occur *after* FDA acts on King's pending labeling supplement. As demonstrated in King's March 18, 2004 Citizen Petition, the pharmacokinetic information in the current approved SKELAXIN® label is essential information for practitioners that impacts the safe and effective prescribing and use of the drug. This information must therefore also appear in the labeling for any generic versions of SKELAXIN® marketed in the future. Accordingly, any Agency decision that this pharmacokinetic information cannot be 'carved out' of generic metaxalone labeling would be well-supported by the administrative record and appropriate. Nevertheless, because changes to the pharmacokinetic section of SKELAXIN® labeling appear imminent, King agrees that Agency resources would be best utilized by delaying

its determination on any proposed carve out until after the specific language of the new pharmacokinetics section of the SKELAXIN® labeling has been approved by FDA.

As explained in the balance of these comments, the criteria for mandatory and discretionary stays in 21 C.F.R. § 10.35(e) are not satisfied, and therefore Mutual's Petition for Stay should be denied.

I. Mutual's Petition Is Frivolous And Is Not Pursued In Good Faith

The thrust of Petitioner's argument is that experts in the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products ("Division") in the Office of Drug Evaluation ("ODE") are on the verge of abrogating their duties. According to Mutual, the Division will "hastily" and mistakenly approve King's supplement using "faulty medical assumptions" unless it has the benefit of Mutual's "scrutiny and comment" on the clinical data submitted by King in support of its supplement. As an initial matter, FDA's review of King's supplement can hardly be characterized as hasty or cursory. King submitted its supplement on April 21, 2003, and FDA responded with an approvable letter eleven months later, on March 12, 2004. Mutual's suggestion that the Division has not carefully evaluated the data and that approval of King's supplement now would constitute precipitous action is simply baseless.

Second, there is no legal basis for Petitioner's demand for access to proprietary clinical data submitted to King's approved NDA and to its pending NDA supplement. It is well established that these data are not available for public disclosure. *See* 21 C.F.R. §§ 314.430, 20.61; 5 U.S.C. 552(b)(4); 21 U.S.C. § 355(l). Apparently recognizing that such information is not disclosable, Mutual argues that King has somehow "opened the door" to public debate of the studies through the filing of its Citizen Petition. This is incorrect. King's Citizen Petition demonstrates that the pharmacokinetic information in the currently approved SKELAXIN® labeling cannot be omitted from the labeling for generic metaxalone without rendering those generic products less safe or effective for their conditions of use, and that it is the burden on any ANDA applicant who wishes to omit such information to provide data sufficient to prove otherwise. Thus, to the extent that public debate has been invited, it is debate about the propriety of omitting information from the currently approved labeling for SKELAXIN®, and of the adequacy of any data generated and presented by the ANDA applicants on this issue, not debate about the King studies which were already evaluated by FDA before approval of the current labeling.[1]

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[1] Relatedly, Mutual also theorizes, based on the numbers used to identify King's studies, that King conducted additional studies numbered 102 and 104 that are unfavorable to King's Citizen Petition. This is incorrect. While a protocol for study 102 was prepared, the study was never conducted. Study 104 compared the bioavailability of one 800 mg tablet of SKELAXIN® with two 400 mg tablets of SKELAXIN® under fasted conditions. The

Third, Mutual's assumption that FDA's NDA review process is, or should be, a public one is faulty. Mutual has no right to involvement in the consideration by the Division of the labeling for SKELAXIN®. While many aspects of the Division's review of the NDA for SKELAXIN® may be of interest to Mutual because they bear on the ease with which Mutual may obtain approval of, or the manner in which Mutual may market, its generic product, the generic drug approval process is entirely derivative to the process of NDA approval. Rather than participate in the NDA approval process, generic companies have the statutory right to benefit from that process by copying pioneer products within the parameters established during that process, and in the Federal Food, Drug and Cosmetic Act ("FFDCA") and FDA's regulations. The FFDCA does not provide for any third party role in the approval process. Members of the public are simply not entitled to act as co-reviewers of a pioneer company's data. The only opportunity for public comment on a pending NDA occurs when FDA determines that Advisory Committee review would be appropriate. FDA has not made this determination here, and instead issued an approvable letter. Accordingly, neither Mutual nor any other member of the public, may interfere in FDA's review of

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study confirmed bioequivalence of the two strengths, and was submitted to FDA in an annual report.

King's data. Should Mutual or others have data of their own potentially relevant to FDA's review, those data may be submitted to FDA via a Citizen Petition.

Fourth, Mutual's assertion that King's data are "dubious" and insufficient to support King's pending supplement is also baseless. As Mutual acknowledges, it has not reviewed King's studies, and therefore its assertions that King's supplement is legally impermissible and anticompetitive, and does not reflect clinically important and relevant information are mere speculation. Indeed, at one time, when it suited its purposes, Mutual took the position that information about the bioavailability of metaxalone was extremely important and warranted a change in the Agency's classification of metaxalone and corresponding ANDA requirements. Specifically, based on testing it conducted, Mutual concluded that there is no *in vitro/in vivo* correlation ("IVIVC") with metaxalone[2] and submitted a Citizen Petition requesting the FDA to reclassify metaxalone as a drug product for which potential or actual bioequivalence problems exist ("bio-problem drug") and to require all ANDA applicants to conduct *in vivo* bioequivalence studies. *See* Mutual Citizen Petition, Docket No. 01P-0117 (March 6, 2001). In support of its Petition, Mutual explained that the rate or extent of drug absorption typically

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[2] Apparently, Mutual was not aware that SKELAXIN® had been eligible for a DESI waiver and mistakenly conducted **both** *in vitro* and *in vivo* bioequivalence studies on its version of metaxalone. During the course of these studies, Mutual realized that there was no IVIVC because, although appearing to be bioequivalent in *in vitro* studies, its product failed bioequivalence criteria in *in vivo* studies. *See* Mutual Citizen Petition, Docket No. 01P-0117.

mediates the side effects most frequently experienced with metaxalone (*i.e.*, nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or irritability). Noting the corresponding public health implications of Mutual's finding that reliance on *in vitro* dissolution as a predictor of *in vivo* performance is not possible, Mutual urged the Agency to require all ANDA applicants to conduct *in vivo* bioequivalence studies. Mutual now appears to argue that significant differences between the rate and extent of metaxalone absorption under fed and fasted conditions do *not* reflect clinically important and relevant information, despite the fact that those differences have been shown with exactly the same types of data as it relied on to support its prior petition. We recognize that, because of the FFDCA requirements that ANDA applicants utilize the same labeling as the pioneer products that they copy, these data now put Mutual in an inconvenient position. The fact that Mutual would so directly contradict its prior position, however, demonstrates Mutual's bad faith in pursuing its current petition. In fact, while Mutual attempts to create doubt about the medical/scientific validity of King's studies, its true position seems to be that FDA should not approve *any* labeling supplement if the change might delay approval of generic products. Relatedly, Mutual seems to believe that if labeling changes are to be made, the Division should draft language specifically designed to permit generic companies to carve out protected information. King is aware of no statute, regulation, or

legislative history suggesting that truthful information that bears on the safe and effective use of a drug product should be omitted from labeling or, if included, purposely worded in such a way as to allow generic companies to avoid having to use that wording in their own labeling and thus potentially to avoid the patent certification requirements established by the Hatch-Waxman amendments. Evaluation by ODE of NDAs and label matters for pioneer drugs should not be tainted by considerations outside of the established NDA approval process and criteria. Instead, FDA's authority and responsibility is to consider matters on the scientific merits in a consistent manner under established NDA review criteria and procedures. *See* 21 U.S.C. § 505(d); 21 C.F.R. §§ 314.105, 314.125.

II. Public Policy Does Not Support The Requested Stay

In support of its public policy arguments, Mutual relies on the supposed overriding public policy favoring availability of generic drug products, yet ignores the competing public policy goals underlying the Hatch-Waxman amendments – encouragement of research and innovation and assuring that generic drugs are equally safe and effective as the pioneer products they copy. King and the prior owner of the SKELAXIN® NDA, Elan, have conducted several studies evaluating the effects of food, age, and gender on the bioavailability of metaxalone and, to date, two patents have issued as a result of this work. These studies have revealed essential information for practitioners that impacts the safe and effective

prescribing and use of the drug. This is precisely the type of important research and innovation Congress intended to encourage and reward.

Moreover, based on FDA's prior interpretation of the statute and regulations in this case, in particular the requirement that generic applicants file paragraph IV certifications to the '128 patent, a number of parties have filed applications and certifications and have begun resolving the relevant patent issues in an orderly fashion as envisioned by Hatch-Waxman.[3] Abandoning this process now disrupts settled expectations and introduces uncertainty into the Hatch-Waxman process.

Finally, granting the relief requested in Mutual's Petition would dramatically alter the manner in which FDA reviews supplements and original NDA and ANDAs. Were Mutual permitted to interfere in FDA's scientific evaluation of King's supplement, other generic companies would demand that same right and routinely seek to intervene in other Agency approval decisions that could conceivably affect the timing or ease of generic approvals or the desirability of the market. The impact would extend not only to FDA decisions on labeling protected by exclusivity or patent, but also to evaluation of other matters, such as

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[3] Mutual's characterization of King's patents as "dubious" is not only incorrect, but also irrelevant to its Petition. The validity and enforceability of patents are evaluated in Federal Court, not by FDA. These issues, as well as the related infringement issues, are being litigated in Federal Court as envisioned by the Hatch-Waxman amendments.

specifications, in-process controls, indications and contraindications, warnings, issuance of a Written Request for pediatric studies, determination of whether studies fairly respond to Written Requests, etc. Moreover, other organizations and companies (*e.g.*, public interest organizations, patient groups) would also seek to take advantage of the opportunity to intervene in such matters. The public policy implications of such a shift in Agency decision making are profound, and include inefficient and lengthy review cycles, resulting in delay in approval of new therapies, delays in implementation of important changes and updates, and corresponding failures to meet PDUFA goals.

III. The Public Health Would Be Harmed By The Requested Stay

King's pending supplement proposes to add important pharmacokinetic information to the labeling for SKELAXIN®, and the public health would be harmed by denying healthcare practitioners access to this critical information. Although Mutual asserts that the pharmacokinetic information in the proposed labeling is not clinically significant, Mutual has not even attempted to satisfy its burden of proving this contention. *See* King Citizen Petition, Docket 2004P-0140, Section II.C.2. (March 18, 2004). The Agency has in the past expressed concern about Petitions, such as Mutual's, which are based only on unsupported claims and allegations. Describing a proposed modification to the Citizen Petition regulations, FDA explained:

> The proposal would also require the citizen petition to be based on more than unsupported claims, allegations, or general descriptions of positions or arguments. Although the existing regulation requires petitioners to provide a full statement of the factual grounds on which the petitioner relies, some petitions contain little or no evidence or support or rely on obsolete, irrelevant, or erroneous information. Thus, the proposal would deter the submission of frivolous or unsupported petitions and petitions which simply disagree with an agency decision regardless of the scientific evidence or legal authority supporting that decision, the importance of the public health policies supporting that decision, or the petitioner's lack of sound scientific evidence or legal authority to support its request.

See Proposed Rule, Citizen Petitions, Actions That Can Be Requested By Petition; Denials, Withdrawals, and Referrals for Other Administrative Action, 64 Fed. Reg. 66822, 66823-24 (Nov. 30, 1999). Mutual has not presented data supporting its contention that pharmacokinetic information describing the relative bioavailabilty of metaxalone when taken with or without food is clinically insignificant. Unless and until such data are presented, FDA should ignore Mutual's unsubstantiated allegations.

In contrast, King has submitted evidence establishing the food, gender, and age effects referenced in its proposed labeling and has also submitted evidence demonstrating that this information is clinically significant. As shown in King's March 18, 2004 Citizen Petition, the pharmacokinetic information in the current SKELAXIN® labeling describing the relative bioavailability of metaxalone when taken with or without food is important to the safe and effective use of the drug,

and its omission from generic labeling is potentially misleading. In addition, information in the approvable proposed revised labeling about gender and age effects, and their interrelation with the food effects, is also important and would impact practitioners' prescribing and use of metaxalone. *See* Elia Decl., ¶¶ 21-26, 29.[4] Moreover, FDA has evaluated the studies underlying King's pending supplement and has concluded that the supplement is approvable, subject to formatting revisions to conform the pharmacokinetic section to the ADME layout now typically used. Despite this, Mutual proposes to delay or prevent altogether the sharing of truthful information that impacts the safe and effective use of metaxalone.[5] Any further delay in making this information widely available to practitioners harms public health.

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[4] Mutual's criticism of King's studies as "clinically inconclusive" is misplaced. The studies in fact provided useful information on the parameters they were designed to evaluate. Mutual fails to recognize that the studies were not designed to establish the precise clinical impact of the bioavailability differences on particular patient populations, and errs in assuming that this is necessary before information is clinically relevant or useful to practitioners.

[5] Mutual's lengthy quote from FDA's Draft Guidance for Industry; *Referencing Discontinued Labeling for Listed Drugs in Abbreviated New Drug Applications* (Oct. 2002) is irrelevant for these same reasons. While the Draft Guidance indicates that minor labeling revisions that do not impact the safe and effective use of the product will not preclude approval of ANDAs, the Draft Guidance also clearly states that omission of protected labeling will not be permitted if it renders the generic drug product less safe or effective than the currently marketed pioneer product. Mutual has not submitted any evidence in this case suggesting that omission of the pharmacokinetic information would not render generic metaxalone products less safe or effective than SKELAXIN®, and although it is not King's burden to do so, King has submitted evidence demonstrating the contrary.

IV. Petitioner Will Not Suffer Irreparable Harm In The Absence Of A Stay

Mutual claims it will suffer irreparable harm in the absence of a stay because it has invested time and money to develop a generic metaxalone product and approval of King's labeling supplement will nullify this investment. As an initial matter, no investments will be "nullified" by FDA's action on King's labeling supplement, Mutual's Petition, or King's Petitions. Like all other pharmaceutical companies, Mutual will begin to enjoy a return on its investment once its product is marketed, whether that occurs in the near term, or after expiration of King's patents. Thus, Mutual's claimed injury is illusory. More importantly, monetary losses do not constitute irreparable injury. *See Wisconsin Gas Co. v. FERC,* 758 F.2d 669, 674 (D.C. Cir. 1985) ("The key word in this consideration is *irreparable*. Mere injuries, however substantial, in terms of money, time and energy necessarily expended in the absence of a stay are not enough.") (emphasis in original) (citations omitted); *Mylan Pharmaceuticals, Inc. et al. v. Henney et al.,* 94 F.Supp.2d 36, 58-59 (D.D.C. 2000) (loss of business opportunity and market share due to FDA refusal to approve ANDA does not constitute irreparable injury).

Conclusion

Based on the foregoing, King respectfully urges the Commissioner to deny Mutual's Petition for Stay.

Respectfully submitted,

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